



## RESEARCH ARTICLE

**REVISED** **Contrasting impact of rural, versus urban, living on glucose metabolism and blood pressure in Uganda [version 2; peer review: 2 approved]**

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**Abstract**

**Background:** The burden of cardiometabolic diseases, including cardiovascular diseases and diabetes, is increasing in sub-Saharan Africa and this has been linked to urbanisation. Helminths, through their immunomodulatory properties, may protect against these disorders. We hypothesised that the rural environment protects against cardiometabolic diseases and that helminths may influence rural-urban disparity of cardiometabolic disease risk.

**Methods:** We compared metabolic parameters of individuals aged  $\geq 10$  years living in rural, high-helminth-transmission and urban, lower-helminth-transmission settings in Uganda. Cross-sectional surveys were conducted in rural Lake Victoria island fishing communities and in urban sub-wards in Entebbe municipality. Helminth infection and outcomes, including insulin resistance (computed using the homeostatic model assessment of insulin resistance [HOMA-IR]), fasting blood glucose, fasting blood lipids, blood pressure, body mass index (BMI), waist and hip circumference, were assessed.

**Results:** We analysed 1,898 rural and 930 urban participants. Adjusting for BMI, exercise, smoking, alcohol intake, age and sex, urban residents had lower mean fasting glucose (adjusted mean difference [95%CI] 0.18 [-0.32, -0.05]  $p=0.01$ ) and HOMA-IR (-0.26 [-

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2

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report



report

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0.40, -0.11]  $p=0.001$ ) but higher blood pressure (systolic, 5.45 [3.75, 7.15]  $p<0.001$ ; diastolic, 1.93 [0.57, 3.29]  $p=0.006$ ). Current helminth infection did not explain the observed differences.

**Conclusions:** In the Ugandan context, living in rural fishing communities may protect against hypertension but worsen glucose metabolism.

### Keywords

Rural, Urban, Metabolic, Hypertension, Diabetes, Insulin resistance, Helminths, Africa

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**REVISED Amendments from Version 1**

We thank the reviewers for the insightful comments. Based on the comments, we have made changes to and updated our article. In the abstract, the conclusion has been refined to make it more specific. To explain the difference in fasting glucose between the urban and rural settings, we have included pancreatic beta cell function as an outcome and reported the results. Occupation, as a possible proxy for activity levels, was added to the adjusted models and the new results from the analyses are presented in [Table 2](#) and [Table 3](#). To further explore the role helminths in any observed differences in metabolic outcomes, the impact of *S. mansoni* infection intensity was analysed and the results are shown in [Table 5](#). In the discussion, we made changes to highlight the relatively young study population and incorporated our previous trial findings. Furthermore, we included the possibility of non-compliance to overnight fasting and emphasised the role of diet and socioeconomic status in partially explaining the differences observed in the two settings.

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**Introduction**

Globally, non-communicable diseases (NCDs) are the leading cause of mortality and disability. In 2016, they contributed to 72.3% of deaths<sup>1</sup>, and cardiometabolic disorders were the top contributors to disability adjusted life years<sup>2</sup>. The World Health Organisation (WHO) estimates that 78% of NCD related deaths occur in low and middle income countries and that the NCD burden is rapidly increasing in these countries<sup>3</sup>. Sub-Saharan Africa, a region undergoing rapid economic growth, is experiencing this epidemiological transition, with the double burden of NCDs and communicable diseases.

The increased NCD burden has been linked to urbanisation and, currently, more than half of the world's population lives in urban areas<sup>4</sup>. Urban living is associated with traditional risk factors for cardiometabolic disease such as diets rich in energy-dense foods and reduced physical activity. This may suggest that the rural environment is protective against cardiometabolic diseases and various data sources confirm this<sup>5-7</sup>. However, there are reports of an increasing or already high burden of NCDs such as hypertension and diabetes in rural areas<sup>8-10</sup> and no difference in burden between urban and rural settings<sup>11</sup>. An increase in body mass index in rural areas has been identified as the main driver of the global epidemic of obesity<sup>12</sup>.

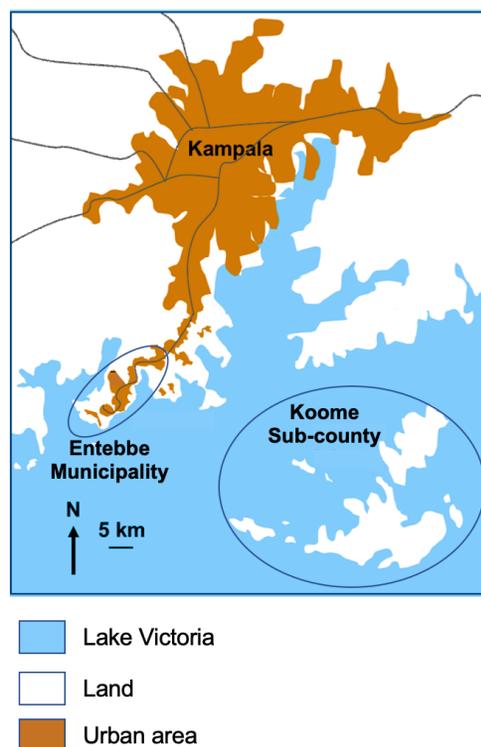
The hygiene hypothesis proposes that the increase in chronic inflammatory disorders in high-income countries is linked to cleaner environments and less exposure to infectious agents<sup>13</sup>. Exposure to infectious agents such as helminths modulates the immune system and may provide protection against these disorders. The urban environment is associated with less exposure to helminths compared to the rural environment. Recently, chronic inflammation has been linked to the aetiology of cardiometabolic disorders such as type 2 diabetes<sup>14</sup> and atherosclerosis<sup>15</sup>, and has been proposed to have a role in essential hypertension<sup>16</sup>. It remains unclear whether reduced exposure

to helminth infections has contributed to the increase, and rural-urban differences, in cardiometabolic disease. There is evidence from animal studies, and the few published human studies, that through their effects on inflammation and metabolism, helminth infections are associated with favourable metabolic outcomes<sup>17-19</sup>.

We therefore tested the hypothesis that the rural environment is protective against metabolic risk factors and diseases and that helminths play a role in this. We investigated differences in metabolic parameters between a rural, high helminth transmission setting and an urban, lower helminth transmission setting in Uganda. We also investigated whether helminths might explain any differences observed between the two settings.

**Methods****Study design and setting**

We conducted parallel cross-sectional surveys, one in a rural and one in an urban setting ([Figure 1](#)). The rural survey was the metabolic outcomes survey of the *Lake Victoria Island Intervention Study on Worms and Allergy-related diseases* (LaVIISWA). LaVIISWA was a cluster-randomised trial investigating the effects of intensive versus standard anthelmintic intervention on health outcomes in 26 rural Lake Victoria island communities of Koome sub-county, Mukono district, Uganda (population, 18,778)<sup>20,21</sup>. The metabolic outcomes survey was conducted between April and November 2017 after four years of the anthelmintic intervention<sup>22</sup>. The survey in the urban setting was deliberately formulated to collect data in parallel with



**Figure 1.** Location of the study areas.

the LaVIISWA outcome surveys to enable rural-urban comparison of allergy-related<sup>23,24</sup> and metabolic outcomes. It was conducted in Entebbe municipality, Wakiso district, Uganda from September 2016 to September 2017. Entebbe municipality is classified by the Uganda Bureau of Statistics as an urban area<sup>25</sup>, and is located on the northern shores of Lake Victoria, with a population of 69,958 residing in 24 sub-wards (the smallest administrative units)<sup>25</sup>.

### Participants

Household surveys were conducted in both settings. Households with members available at the time of conducting the surveys were eligible for inclusion. In the rural setting, the study team, in collaboration with the local leaders, maintained an updated register of all the households in the 26 study villages. This was used as a sampling frame to randomly select 70 households in each of the 26 study villages using Stata software (College Station, Texas, USA). In the urban setting, a different sampling technique was used because resources and time could not permit a complete household listing before starting the survey. With the help of locally available maps, we mapped each sub-ward onto satellite imagery of the area excluding areas that were uninhabited. The mapped sub-wards were then divided into segments of equal geographical size based on lines of latitude and longitude (degrees, minutes, seconds position format) and each segment was numbered. Using random number generation, segments were randomly selected from each sub-ward. The number of segments selected was proportional to the population size of the sub-ward. The midpoint of each selected segment was identified by its coordinates using a geographic information system (GIS) device (eTrex®, Garmin™ Ltd, Kansas, United States). This was used as the starting point for sampling households and the nearest house was selected for inclusion. Houses were then sequentially selected, the next house to be sampled being the nearest to the previous house. In total, 120 geographical segments were targeted in the 24 sub-wards and in each segment, four households were targeted. If a household was empty or refused, the next one was approached until the number per segment was completed.

In both surveys, a household was defined as a habitable roofed structure whose primary function was residence or, if used for dual purposes, had at least one active resident using the structure as their primary residence. In selected and participating households, permission was sought from the household head or another adult in the household if the household head was absent. Households where all members refused to participate, or where all members were absent during the survey period, were excluded. All survey questions are described in the Codebook of the *Underlying data*<sup>26</sup>.

### Variables

The exposure variables were the rural/urban setting and helminth infection status. The outcomes were insulin resistance (measured using the homeostatic model assessment of insulin resistance (HOMA-IR;  $\text{HOMA-IR} = \text{fasting serum insulin} \times \text{fasting glucose} / 22.5$ ), fasting blood glucose, total cholesterol, triglyceride levels, High Density Lipoprotein (HDL) - cholesterol and

low density lipoprotein (LDL) – cholesterol, blood pressure, body mass index (BMI), waist and hip circumference. Following a reviewer's suggestion, we also included mean pancreatic beta cell function (HOMA-B) as an outcome. HOMA-B was calculated using the formula,  $\text{HOMA-B} = (20 \times \text{fasting insulin} (\mu\text{U/ml}) / \text{fasting glucose (mmol/ml)} - 3.5)$ .

### Data sources/ study procedures

The tools and procedures of both surveys were aligned to allow comparison of the metabolic outcomes data between urban and rural settings. A questionnaire was administered to consenting household members. With this questionnaire, data were collected on household and individual sociodemographic characteristics as well as information on lifestyle, exercise or vigorous physical activity, diet, history of diabetes and hypertension.

A physical examination was performed and information obtained on blood pressure, weight, height, waist and hip circumference. With the participant seated, rested and comfortable, blood pressure was measured using a digital sphygmomanometer (OMRON Model M2[hem-7121-E], Omron Health Care, Kyoto, Japan). Three blood pressure measurements were taken five minutes apart, with the average of the last two measurements used for the analysis. A portable, flat digital weighing scale (SECA model 875 7021094, Hamburg, Germany) was used to take two measurements of body weight for each participant and the average of the two readings computed and used in the analysis. Height was measured using a stadiometer (SECA model 213 1721009, Hamburg, Germany) and recorded to the nearest millimetre. Two readings were obtained and the mean was used in the analysis. Quality control checks, using standard calibration rods for the stadiometers and standard weights for the weighing scales, were performed at the beginning of each working day. The sphygmomanometers were calibrated by the Uganda Bureau of Standards.

After an overnight fast, participants provided venous blood samples. The tests carried out on these samples included fasting blood glucose, insulin, fasting lipid profile and haemoparasitology. Fasting blood glucose, insulin and fasting lipid profile were tested using the COBAS *cobas* 6000 analyser (*cobas c* 501 module, Roche Diagnostics, Rotkreuz, Switzerland). *Mansonella perstans* was tested using the modified Knott's method<sup>27</sup>.

Each participant was requested to provide one stool sample. Duplicate slides were made from each sample and the slides independently examined using the Kato Katz technique<sup>28</sup> by experienced technicians. Additionally, real-time stool polymerase chain reaction (PCR) was used to detect *Schistosoma mansoni*, *Necator americanus* and *Strongyloides stercoralis*<sup>29,30</sup>.

Diabetes and impaired fasting glucose were defined, according to the WHO classification, as fasting plasma glucose of  $\geq 7.0$  mmol/L and 6.1–6.9 mmol/L, respectively<sup>31,32</sup>. Hypertension was defined as diastolic blood pressure of  $\geq 90$  mmHg or systolic blood pressure of  $\geq 140$  mmHg in participants

≥18 years of age<sup>33</sup>. Participants <18 years old were categorised to be hypertensive if their systolic or diastolic blood pressures were above the 95<sup>th</sup> percentile using the Centers for Disease Control blood pressure charts for children and adolescents<sup>34</sup>.

### Sample size

In the rural setting, we aimed to recruit 1950 participants (sampling 70 households without replacement was expected to yield 75 participants aged ≥10 years from each of the 26 villages). This number was primarily calculated for the LaVIISWA trial analysis and was estimated to give 80% power to detect a difference in mean HOMA-IR of 0.05 between the trial arms assuming an intra-cluster correlation coefficient of 0.03 and a standard deviation on the log scale of 0.2. In the urban survey, we targeted a sample size of 960 individuals aged ten and over, and estimated that this would allow us to detect an absolute difference of 0.03 in mean HOMA-IR between urban and rural settings, assuming a standard deviation on the log scale of 0.2, and a design effect of 1.5. Assuming a 13% failure rate in household response and an average of around 2.3 individuals aged ≥10 years per household 480 households were targeted.

### Statistical methods

The statistical analyses were performed using Stata version 13.0 (College Station, Texas, USA). We tabulated the characteristics of households and individuals in the urban setting alongside those of the rural setting in order to see how these differed between the two settings. We compared the outcomes between the rural setting and the urban setting. We summarised the mean for each outcome in the two settings and then assessed for differences by fitting regression models for each outcome that included a random effect to allow for the clustering (by village for the rural setting, by sub-ward for the urban setting) and a binary covariate that denoted whether the individual is in the urban or rural setting. Crude and adjusted mean differences and 95% confidence intervals are presented. All the outcomes were initially adjusted for age and sex and further adjusted for occupation, exercise, alcohol intake and smoking. HOMA-IR, fasting glucose, triglycerides, LDL-cholesterol, HDL-cholesterol, systolic and diastolic blood pressure were additionally adjusted for BMI. We did not perform any adjustments for multiple testing. In all analyses, data from the rural setting comprised all participants regardless of whether they had received intensive or standard anthelmintic treatment, i.e. both arms of the LaVIISWA trial were included. This was done because there were no strong differences in the outcomes between the trial arms<sup>22</sup>.

To investigate whether helminths influence the differences observed in the metabolic outcomes, each helminth variable was added separately to the model and any change in the mean difference, confidence interval and p-values were assessed. Helminths were considered to have an influence on the urban-rural differences if addition of the variable resulted in a substantial change in the mean difference.

### Ethical approval and consent

Ethical approval was granted by the Uganda Virus Research Institute Research Ethics committee (reference number GC/127/17/01/573), the Uganda National Council for Science and Technology (reference number HS 2185) and the London School

of Hygiene and Tropical Medicine (reference number 9917). Permission to conduct the surveys was granted by the local leadership of Mukono district (for the rural survey) and Entebbe municipality (for the urban survey). All participating adults and emancipated minors provided written informed consent. Participants aged 10 to 17 years provided assent and their parents/guardians provided written informed consent.

## Results

### Participants

The survey flow is shown in [Figure 2](#). In the rural setting, 2167 individuals aged 10 years and above from 1271 households were eligible for participation. Of these, 1898/2167 (87.6%) consented and provided data. In the urban setting, 1124 individuals from 416 households were eligible and 930/1124 (82.7%) consented and provided data. One sub-ward was a military facility and could not be surveyed because the study team was not granted access. In both surveys, the main reasons for non-participation were absenteeism (180/2167;8.3% in the rural setting and 165/1124;14.7% in the urban setting) and refusal (80/2167;3.7% in the rural setting and 18/1124;1.6% in the urban setting). Individual-level demographic data and survey responses are available as *Underlying data*<sup>26</sup>.

### Descriptive data

The characteristics of the study participants are shown in [Table 1](#). Male participants constituted approximately half (51%; 1010/1890) and 35% (322/920) of the participants in the rural and urban survey respectively. The mean age of the participants was 31.5 years in the rural setting and 29.7 years in the urban setting. In the rural survey, the main economic activity was fishing (739/1898;37.9%) while in the urban setting most participants were involved in service provision, were artisans or had shops and salons (211/917;23.9%). The rural population was more physically active with 49.3% (920/1868) reporting exercise or vigorous physical activity at least once a week compared to 16.6% (152/914) in the urban setting. More participants in the rural setting reported having ever smoked (343/1868;18.3% vs 38/914;4.2%) or taken alcohol (905/1868;47.5% vs 187/914;20.5%) compared to those in the urban setting.

The rural participants had more exposure to the lake with 67.5% (1309/1857) reporting daily lake contact compared to only 3.3% (30/916) in the urban setting. Regarding anthelmintic treatment, 86.9% (1661/1896) of participants in the rural setting reported having ever received treatment for worms compared to 72.8% (646/888) of urban participants. Of these, 67.2% (1113/1604) in the rural setting reported having been treated with praziquantel in the last 12 months compared to 3.0% (19/639) in the urban setting. Helminth prevalence was higher in the rural setting with a significantly higher prevalence of *S. mansoni* (stool Kato Katz, 31.7% vs 9.9%, p<0.001; stool PCR 47.6% vs 22.2%, p<0.001), *Trichuris trichiura* (stool Kato Katz, 6.9% vs 2.2%, p=0.002) and *Strongyloides stercoralis* (stool PCR, 6.1% vs 3.2%, p=0.026). In both settings, most of the *S. mansoni* infections were of light intensity.

### Rural-urban differences in metabolic outcomes

The metabolic outcomes measured in both settings are shown in [Table 2](#). Mean fasting glucose was higher in the rural setting

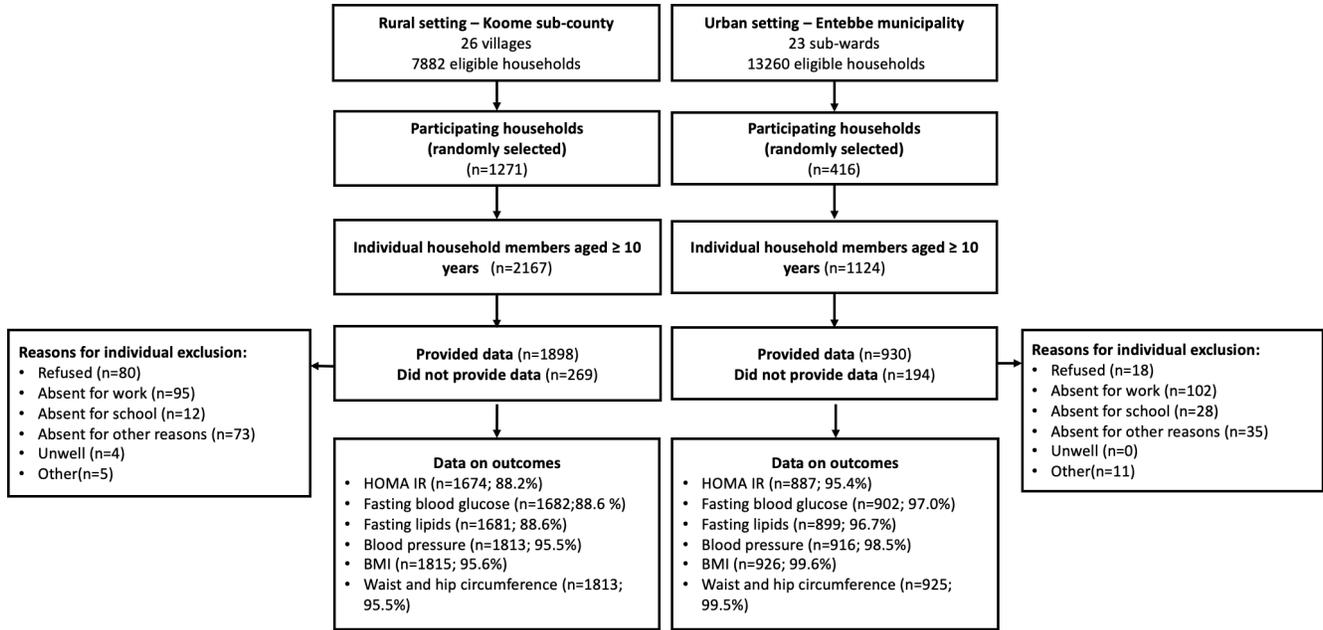


Figure 2. Study flow chart.

Table 1. Characteristics of participants in the rural and urban settings.

	Rural setting n/N (%)	Urban setting n/N (%)	P value*
<b>Household-level characteristics</b>			
Total number of households participating in the survey	1271	416	
Household size (median, IQR)	2 (1,3)	4 (2,5)	
<b>Individual-level characteristics</b>			
Sex, male	1010/1898 (51.2)	322/920 (35.0)	<0.001
Age			
Age in years (mean, SD)	31.5 (11.0)	29.7 (15.0)	0.003
Age in years, grouped			
10–19	215/1898 (11.8)	261/920 (28.4)	<0.001
20–29	648/1898 (33.7)	298/920 (32.4)	
30–39	594/1898 (30.7)	164/920 (17.8)	
40+	441/1898 (23.7)	197/920 (21.4)	
Occupation			
Child/student	121/1898 (7.2)	253/917 (27.6)	<0.001
Housewife	199/1898 (9.7)	166/917 (18.0)	
Fishing or lake related	739/1898 (37.9)	17/917 (1.9)	
Shops, salons, artisans, service providers	214/1898 (13.0)	211/917 (23.9)	
Bars, restaurants, food providers, entertainment	160/1898 (8.4)	48/917 (5.2)	
Agriculture, lumbering, charcoal	396/1898 (19.2)	35/917 (3.8)	
Professional	33/1898 (2.3)	37/917 (4.0)	
Unemployed	36/1898 (2.4)	128/917 (14.0)	
Other (not specified)	0	22/917 (2.4)	

Household-level characteristics	Rural setting n/N (%)	Urban setting n/N (%)	P value*
Residence			
Always lived in the study area	164/1898 (8.6)	454/919 (49.4)	<0.001
Place of birth			
Village	1716/1898 (90.2)	318/918 (34.6)	<0.001
Town or city	182/1898 (9.8)	600/918 (65.4)	
First five years			
Village	1700/1885 (89.8)	339/918 (36.9)	<0.001
Town or city	185/1885 (10.2)	579/918 (63.1)	
Age of participant when he/she moved to this village (mean, SD)	23.0 (11.2)	22.8 (11.3)	0.388
Parental tribe			
Maternal tribe region of origin			
Central	678/1898 (36.7)	400/918 (43.5)	0.097
Western	294/1898 (15.3)	190/918 (20.7)	
Eastern	405/1898 (21.0)	131/918 (14.3)	
Northern	202/1898 (10.1)	110/918 (12.0)	
Non-Ugandan	311/1898 (16.6)	81/918 (8.8)	
Do not know	8/1898 (0.4)	6/918 (0.7)	
Paternal tribe region of origin			
Central	751/1898 (39.1)	404/918 (44.0)	0.202
Western	328/1898 (17.6)	172/918 (18.7)	
Eastern	385/1898 (20.6)	152/918 (16.6)	
Northern	201/1898 (10.3)	115/918 (12.5)	
Non-Ugandan	230/1898 (12.2)	71/918 (7.7)	
Do not know	3/1898 (0.2)	4/918 (0.4)	
Treatment for worms			
Ever treated for worms	1661/1896 (86.9)	646/888 (72.8)	<0.001
Treated with albendazole in the last 12 months	1301/1597 (82.1)	480/641 (74.9)	0.666
Treated with praziquantel in the last 12 months	1113/1604 (67.2)	19/639 (3.0)	<0.001
Lake contact			
Frequency of lake contact			
Every day	1309/1857 (67.5)	30/916 (3.3)	<0.001
Almost every day	297/1857 (16.3)	36/916 (3.9)	
Once a week	192/1857 (11.9)	44/916 (4.8)	
Once a month	52/1857 (3.8)	120/916 (13.1)	
Less than once a month	7/1857 (0.6)	686/916 (74.9)	

Household-level characteristics	Rural setting n/N (%)	Urban setting n/N (%)	P value*
Diabetes			
History of diabetes			
Yes	7/1868 (0.5)	26/914 (2.8)	<0.001
No	1841/1868 (98.7)	808/914 (88.4)	
Do not know	20/1868 (0.9)	80/914 (8.8)	
Hypertension			
History of hypertension			
Yes	44/1868 (3.0)	77/914 (8.4)	<0.001
No	1815/1868 (96.5)	811/914 (88.7)	
Do not know	9/1868 (0.5)	26/914 (2.8)	
Exercise			
How often do you exercise / participate in vigorous physical activity			
Every day	28/1868 (1.4)	11/914 (1.2)	<0.001
Almost every day	396/1868 (21.1)	53/914 (5.8)	
Once a week	496/1868 (27.3)	88/914 (9.6)	
Once a month	372/1868 (18.7)	90/914 (9.9)	
Less than once a month	576/1868 (31.5)	672/914 (73.5)	
History of smoking and alcohol intake			
Ever smoked (either pipe or cigarette)	343/1868 (18.3)	38/914 (4.2)	<0.001
Ever taken alcohol	905/1868 (47.5)	187/914 (20.5)	<0.001
Helminth infections			
<i>Schistosoma mansoni</i> , stool Kato Katz	440/1505 (31.7)	76/770 (9.9)	<0.001
<i>Schistosoma mansoni</i> intensity, stool Kato Katz			
Uninfected	1065/1505 (68.3)	694/770 (90.1)	<0.001
Light	230/1505 (16.6)	36/770 (4.7)	
Moderate	121/1505 (8.6)	27/770 (3.5)	
Heavy	89/1505 (6.5)	13/770 (1.7)	
<i>Schistosoma mansoni</i> , stool PCR	694/1487 (47.6)	171/771 (22.2)	<0.001
Hookworm, stool Kato Katz	39/1505 (2.4)	25/769 (3.3)	0.308
Hookworm, stool PCR	55/1364 (3.7)	43/771 (5.6)	0.145
<i>Trichuris trichiura</i> , stool Kato Katz	122/1505 (6.9)	17/770 (2.2)	0.002
<i>Ascaris lumbricoides</i> , stool Kato Katz	3/1505 (0.2)	0	-
<i>Mansonella perstans</i> , modified Knott's	20/1677 (1.1)	3/918 (0.3)	0.143
<i>Strongyloides stercoralis</i> , stool PCR	101/1486 (6.1)	25/771 (3.2)	0.026

Percentages adjusted for survey design; \*P values obtained from survey design-based regression.

than in the urban setting (4.81 vs 4.71 mmol/L; adjusted mean difference -0.26 [95% confidence interval -0.40, -0.11] p=0.001). In unadjusted analyses and following adjustment for age and sex, no differences were seen in HOMA-IR. However, after further

adjustment for BMI, exercise, alcohol intake and smoking, there was a negative mean difference suggesting higher HOMA-IR in the rural setting. The mean difference was most altered by adjusting for BMI. Following inclusion of HOMA-B as an

**Table 2. Comparison of metabolic outcomes in the urban and rural settings.**

Outcome	Mean		Crude mean difference (95% CI)	P-value	*Adjusted mean difference (95% CI)	*P-value	**Adjusted mean difference (95% CI)	**P-value
	Rural	Urban						
HOMA - IR	GM 1.86	GM 2.40	0.08 (-0.07, 0.23)	0.28	-0.02 (-0.16, 0.13)	0.79	<b>-0.18 (-0.32, -0.05)</b>	<b>0.01</b>
Fasting glucose (mmol/L)	4.81	4.71	-0.10 (-0.20, 0.00)	0.05	-0.10 (-0.20, 0.01)	0.06	<b>-0.26 (-0.40, -0.11)</b>	<b>0.001</b>
Fasting insulin ( $\mu$ U/ml)	GM 66.99	GM 87.26	0.12 (-0.03, 0.26)	0.11	0.01 (-0.12, 0.15)	0.84	-0.12 (-0.25, 0.01)	0.06
Triglycerides (mmol/L)	1.10	1.16	0.07 (-0.05, 0.19)	0.27	0.10 (-0.03, 0.22)	0.12	0.10 (-0.03, 0.23)	0.12
Total cholesterol (mmol/L)	4.48	4.58	0.10 (-0.21, 0.40)	0.53	0.12 (-0.18, 0.41)	0.42	0.15 (-0.14, 0.44)	0.31
LDL - Cholesterol (mmol/L)	2.66	2.85	0.19 (-0.22, 0.60)	0.35	0.19 (-0.22, 0.60)	0.35	0.21 (-0.27, 0.70)	0.37
HDL - Cholesterol (mmol/L)	1.42	1.31	-0.11 (-0.35, 0.12)	0.34	-0.10 (-0.33, 0.13)	0.38	-0.07 (-0.37, 0.23)	0.63
Systolic blood pressure (mmHg)	114.21	117.28	3.07 (1.60, 4.53)	<0.001	<b>5.66 (4.35, 6.96)</b>	<b>&lt;0.001</b>	<b>5.45 (3.75, 7.15)</b>	<b>&lt;0.001</b>
Diastolic blood pressure (mmHg)	75.81	76.49	0.67 (-0.45, 1.80)	0.24	<b>2.23 (1.26, 3.21)</b>	<b>&lt;0.001</b>	<b>1.93 (0.57, 3.29)</b>	<b>0.006</b>
Body mass index (kg/m <sup>2</sup> )	23.40	23.83	0.43 (-0.12, 0.97)	0.12	<b>0.81 (0.40, 1.23)</b>	<b>&lt;0.001</b>	<b>1.07 (0.59, 1.54)</b>	<b>&lt;0.001</b>
Waist circumference (cm)	80.44	78.95	-1.49 (-3.42, 0.43)	0.13	0.24 (-1.35, 1.82)	0.77	0.24 (-1.71, 2.19)	0.81
Waist-hip Ratio	GM 0.68	GM 0.71	0.02 (-0.01, 0.05)	0.26	0.02 (-0.01, 0.05)	0.11	0.03 (-0.01, 0.06)	0.17

HOMA-IR, Homeostatic model assessment of insulin resistance; GM, geometric means; P values obtained from survey design-based linear regression; \*Adjusted for age and sex; \*\*Adjusted for age, sex, occupation, exercise, alcohol intake and smoking; HOMA-IR, fasting glucose, triglycerides, LDL-cholesterol, HDL-cholesterol, systolic and diastolic BP were additionally adjusted for BMI.

additional outcome at the suggestion of a review, we found that individuals in the rural setting had lower (worse) pancreatic beta cell function than individuals in the urban setting even after adjusting for age, sex, exercise, alcohol intake, smoking and BMI (141.34 vs 201.72; 40.36 [8.00, 72.72]  $p=0.02$ ).

Participants in the rural setting had significantly lower mean blood pressure than those in the urban setting even after adjustment for sex, age, exercise, alcohol, smoking and BMI (systolic blood pressure, 114.21 vs 117.28 mmHg 5.45 [3.75, 7.15]  $p<0.001$ ; diastolic blood pressure 75.81 vs 76.49 mmHg, 1.93 [0.57, 3.29]  $p=0.006$ ). These differences in blood pressure were more marked in the older age groups (Figure 3).

Participants in the rural setting had lower mean BMI than those in the urban setting. No differences were observed for waist circumference, waist-hip ratio, triglycerides, total cholesterol, LDL-cholesterol or HDL-cholesterol.

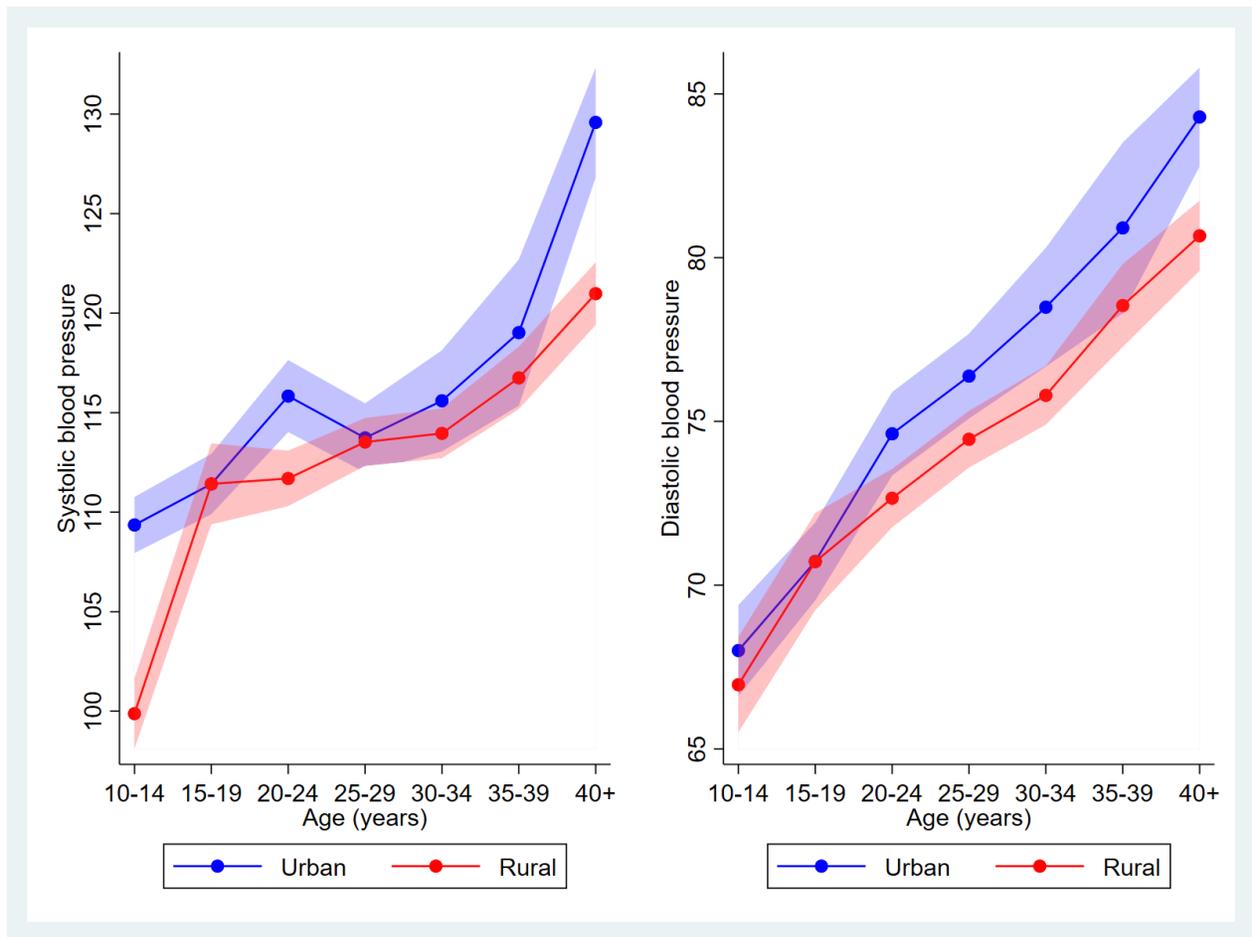
Despite having, on average, higher fasting glucose in the rural setting, there was no difference in the prevalence of diabetes between the rural and urban settings after adjusting for multiple

potential confounders. However, the rural setting had a lower prevalence of hypertension (9.1% vs 13.4%,  $p=0.01$ ) and obesity (7.7% vs 14.0%,  $p<0.001$ ), than the urban setting (Table 3 and Table 4).

Helminth infection and intensity did not explain the rural urban differences observed for the metabolic parameters: very little change was seen in the mean differences after further adjustment for helminth infection status or helminth infection intensity (Table 5).

## Discussion

In this paper, we have shown that individuals in a rural, high helminth transmission setting had higher mean HOMA-IR and fasting glucose, and lower pancreatic beta cell function than those in an urban low helminth transmission setting. They also had substantially lower blood pressure and BMI than their urban counterparts. This was not explained by differences in activity levels, age or sex or (for blood pressure) BMI and we did not find any impact of helminth infection on the observed rural-urban differences.



**Figure 3. Variation of mean systolic and diastolic blood pressure with age in the rural and urban settings.** The shaded areas represent 95% confidence intervals (allowing for clustering) around the mean systolic and diastolic blood pressure measurements for each age group.

**Table 3. Comparison of metabolic outcomes by disease categories.**

Outcome	n/N (%)		Crude odds ratios (95% CI)	P-value	*Adjusted odds ratios (95% CI)	*P-value	**Adjusted odds ratios (95% CI)	**P-value
	Rural	Urban						
Diabetes (FBG $\geq$ 7 mmol/l)	16/1681 (1.0)	22/902 (2.4)	2.41 (1.32, 4.40)	0.01	<b>2.45 (1.31, 4.58)</b>	<b>0.01</b>	1.84 (0.79, 4.27)	0.15
Impaired fasting glucose (FBG 6.1 – 6.9 mmol/l)	35/1681 (1.9)	14/902 (1.6)	0.84 (0.39, 1.81)	0.66	0.92 (0.42, 2.06)	0.84	1.05 (0.42, 2.63)	0.92
Hypertension***	156/1813 (9.1)	123/916 (13.4)	1.60 (1.14, 2.25)	0.01	<b>2.36 (1.67, 3.34)</b>	<b>&lt;0.001</b>	<b>1.81 (1.15, 2.83)</b>	<b>0.01</b>
Prehypertension	574/1813 (30.7)	285/916 (31.1)	1.10 (0.89, 1.36)	0.36	<b>1.58 (1.26, 1.98)</b>	<b>&lt;0.001</b>	<b>1.64 (1.16, 2.33)</b>	<b>0.01</b>
Obese (BMI $\geq$ 30)	128/1815 (7.7)	130/926 (14.0)	2.34 (1.70, 3.22)	<0.001	<b>2.28 (1.60, 3.23)</b>	<b>&lt;0.001</b>	<b>2.36 (1.55, 3.60)</b>	<b>&lt;0.001</b>
Overweight (BMI 25.0 – 29.9)	349/1815 (19.9)	188/926 (20.3)	1.30 (0.99, 1.70)	0.06	1.33 (1.00, 1.77)	0.05	1.45 (0.96, 2.17)	0.08
Underweight (BMI <18.5)	119/1815 (7.0)	132/926 (14.3)	2.61 (1.72, 3.96)	<0.001	<b>1.54 (1.04, 2.29)</b>	<b>0.03</b>	1.00 (0.56, 1.78)	0.99
Central (abdominal) obesity (WC $\geq$ 94cm males, WC $\geq$ 80cm females)	511/1813 (29.7)	321/925 (34.7)	1.26 (0.94, 1.68)	0.12	1.15 (0.83, 1.59)	0.38	1.32 (0.86, 2.04)	0.20
Central (abdominal) obesity (WHR>0.9 males, WHR>0.85 females)	505/1813 (27.8)	227/925 (24.5)	0.84 (0.63, 1.12)	0.24	0.75 (0.55, 1.02)	0.06	0.74 (0.53, 1.03)	0.08
Metabolic Syndrome****	109/1675 (6.4)	77/908 (8.5)	1.37 (0.88, 2.13)	0.16	1.30 (0.83, 2.04)	0.24	0.74 (0.53, 1.03)	0.08

FBG, Fasting Blood Glucose; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; BMI, Body Mass Index; WC, Waist Circumference; WHR, Waist Hip Ratio; \*Adjusted for age and sex; P values obtained from survey design-based logistic regression; \*\*Adjusted for age, sex, occupation, exercise, alcohol intake and smoking; diabetes, impaired fasting glucose, hypertension and prehypertension were additionally adjusted for BMI; \*\*\* SBP  $\geq$  140mmHg or DBP  $\geq$  90mmHg for adults; Blood pressure  $\geq$ 90<sup>th</sup> percentile for participants aged 10-17 years; \*\*\*\*Any three of: Central obesity [WC $\geq$ 94cm males WC  $\geq$ 80cm Females], FBG>5.55, [SBP $\geq$ 130 or DBP $\geq$ 85], Elevated Triglycerides [ $\geq$ 1.7 mmol/L], Reduced HDL – Cholesterol [ $<$ 1 mmol/L Males,  $<$ 1.3 mmol/L females].

**Table 4. Comparison of metabolic outcomes by disease categories in adult participants (aged ≥18 years).**

Outcome	n/N (%)		Crude odds ratios (95% CI)	P-value	*Adjusted odds ratios (95% CI)	*P-value
	Rural	Urban				
Diabetes (FBG ≥ 7 mmol/l)	16/1551 (1.1)	21/716 (2.9)	2.66 (1.45, 4.89)	0.002	<b>2.34 (1.24, 4.40)</b>	<b>0.01</b>
Impaired fasting glucose (FBG 6.1 – 6.9 mmol/l)	33/1551 (1.9)	12/716 (1.7)	0.89 (0.40, 2.01)	0.78	0.94 (0.41, 2.13)	0.87
Hypertension**	152/1678 (9.5)	116/727 (16.0)	2.01 (1.46, 2.77)	<0.001	<b>2.62 (1.86, 3.69)</b>	<b>&lt;0.001</b>
Obese (BMI ≥ 30)	127/1679 (8.3)	128/732 (17.5)	2.64 (1.92, 3.64)	<0.001	<b>2.31 (1.64, 3.26)</b>	<b>&lt;0.001</b>
Overweight (BMI 25.0 – 29.9)	346/1679 (21.4)	177/732 (24.2)	1.41 (1.08, 1.84)	0.01	1.32 (1.00, 1.74)	0.05
Underweight (BMI < 18.5)	51/1679 (3.2)	33/732 (4.5)	1.73 (0.96, 3.14)	0.07	1.90 (1.08, 3.36)	0.03
Central (abdominal) obesity (WC ≥ 94cm males, WC ≥ 80cm females)	505/1677 (31.9)	310/731 (42.4)	1.57 (1.17, 2.13)	0.004	1.18 (0.85, 1.63)	0.32
Central (abdominal) obesity (WHR > 0.9 males, WHR > 0.85 females)	471/1677 (28.2)	202/731 (27.6)	0.97 (0.73, 1.29)	0.85	0.80 (0.59, 1.08)	0.14
*** Metabolic Syndrome	108/1547 (6.9)	76/719 (10.6)	1.59 (1.04, 2.44)	0.03	1.30 (0.84, 2.02)	0.24

FBG, Fasting Blood Glucose; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; BMI, Body Mass Index; WC, Waist Circumference; WHR, Waist Hip Ratio; \*Adjusted for age and sex; P values obtained from survey design-based logistic regression; \*\* SBP ≥ 140mmHg or DBP ≥ 90mmHg for adults; Blood pressure ≥ 90<sup>th</sup> percentile for participants aged 10–17 years; \*\*\* Any three of: Central obesity [WC ≥ 94cm males WC ≥ 80cm females], FBG > 5.55, [SBP ≥ 130 or DBP ≥ 85], Elevated Triglycerides [≥ 1.7 mmol/L], Reduced HDL – Cholesterol [ $< 1$  mmol/L Males,  $< 1.3$  mmol/L females].

Table 5. Effect of adjusting for helminths on differences in metabolic outcomes.

Outcome	Mean		Crude mean difference (95% CI)	P-value	*Adjusted mean difference (95% CI)	*P-value	**Adjusted mean difference (95% CI)	**P-value
	Rural	Urban						
<b>HOMA - IR</b>	GM 1.86	GM 2.40	0.08 (-0.07, 0.23)	0.28	-0.02 (-0.16, 0.13)	0.79	<b>-0.13 (-0.25, -0.01)</b>	<b>0.04</b>
With each helminth included in the model								
<i>S. mansoni</i> KK (n=2092)			0.07 (-0.08, 0.21)	0.38	-0.01 (-0.15, 0.14)	0.95	-0.12 (-0.25, 0.02)	0.09
<i>S. mansoni</i> PCR (n=2077)			0.05 (-0.10, 0.19)	0.54	-0.03 (-0.17, 0.11)	0.70	-0.13 (-0.25, 0.00)	0.06
<i>S. mansoni</i> intensity KK (n=2092)			0.07 (-0.08, 0.21)	0.37	0.00 (-0.15, 0.14)	0.97	-0.11 (-0.24, 0.02)	0.09
<i>T. trichiura</i> KK (n=2092)			0.08 (-0.07, 0.22)	0.32	-0.02 (-0.16, 0.13)	0.82	-0.12 (-0.25, 0.01)	0.07
Hookworm PCR (n=1962)			0.07 (-0.08, 0.22)	0.33	-0.02 (-0.16, 0.13)	0.82	-0.12 (-0.25, 0.02)	0.08
<i>S. stercoralis</i> PCR (n=2076)			0.06 (-0.09, 0.21)	0.41	-0.02 (-0.17, 0.13)	0.78	-0.12 (-0.26, 0.01)	0.06
Any worm (n=2028)			0.05 (-0.10, 0.19)	0.54	-0.03 (-0.17, 0.11)	0.66	-0.13 (-0.25, 0.00)	0.05
<b>Fasting glucose (mmol/L)</b>	4.81	4.71	-0.10 (-0.20, 0.00)	0.05	-0.10 (-0.20, 0.01)	0.06	<b>-0.13 (-0.24, -0.01)</b>	<b>0.04</b>
With each helminth included in the model								
<i>S. mansoni</i> KK (n= 2109)			-0.10 (-0.22, 0.02)	0.09	-0.07 (-0.19, 0.04)	0.21	-0.11 (-0.23, 0.02)	0.08
<i>S. mansoni</i> PCR (n=2094)			-0.12 (-0.24, 0.00)	0.05	-0.10 (-0.21, 0.02)	0.11	-0.13 (-0.25, 0.00)	0.04
<i>S. mansoni</i> intensity KK (n=2109)			-0.10 (-0.22, 0.02)	0.10	-0.07 (-0.19, 0.04)	0.22	-0.11 (-0.23, 0.02)	0.09
<i>T. trichiura</i> KK (n=2109)			-0.08 (-0.19, 0.03)	0.14	-0.08 (-0.19, 0.03)	0.17	-0.11 (-0.23, 0.01)	0.07
Hookworm PCR (n=1979)			-0.08 (-0.19, 0.03)	0.15	-0.07 (-0.18, 0.04)	0.20	-0.11 (-0.23, 0.02)	0.09
<i>S. stercoralis</i> PCR (n=2093)			-0.08 (-0.19, 0.04)	0.194	-0.07 (-0.19, 0.04)	0.20	-0.11 (-0.23, 0.02)	0.09
Any worm (n=2045)			-0.12 (-0.25, 0.01)	0.06	-0.10 (-0.22, 0.03)	0.12	-0.13 (-0.26, 0.00)	0.05
<b>Systolic blood pressure (mmHg)</b>	114.21	117.28	3.07 (1.60, 4.53)	<0.001	5.66 (4.35, 6.96)	<0.001	4.64 (3.23, 6.06)	<0.001
With each helminth included in the model								
<i>S. mansoni</i> KK (n=2187)			3.47 (1.93, 5.01)	<0.001	5.94 (4.51, 7.38)	<0.001	4.66 (2.93, 6.39)	<0.001
<i>S. mansoni</i> PCR (n=2172)			3.45 (1.99, 4.92)	<0.001	5.82 (4.58, 7.06)	<0.001	4.67 (3.16, 6.19)	<0.001
<i>S. mansoni</i> intensity KK (n=2187)			3.47 (1.95, 5.00)	<0.001	5.94 (4.53, 7.36)	<0.001	4.65 (2.96, 6.34)	<0.001
<i>T. trichiura</i> KK (n=2187)			3.10 (1.75, 4.45)	<0.001	5.65 (4.37, 6.92)	<0.001	4.45 (2.89, 6.00)	<0.001
Hookworm PCR (n=2054)			3.42 (1.98, 4.86)	<0.001	5.88 (4.58, 7.18)	<0.001	4.64 (3.11, 6.18)	<0.001
<i>S. stercoralis</i> PCR (n=2171)			3.49 (2.10, 4.89)	<0.001	5.83 (4.55, 7.11)	<0.001	4.65 (3.13, 6.18)	<0.001
Any worm (n=2122)			3.30 (1.90, 4.70)	<0.001	5.71 (4.49, 6.92)	<0.001	4.53 (3.04, 6.03)	<0.001

Outcome	Mean		Crude mean difference (95% CI)	P-value	*Adjusted mean difference (95% CI)	*P-value	**Adjusted mean difference (95% CI)	**P-value
	Rural	Urban						
<b>Diastolic blood pressure (mmHg)</b>	75.81	76.49	0.67 (-0.45, 1.80)	0.24	2.23 (1.26, 3.21)	<0.001	1.89 (0.81, 2.97)	0.001
With each helminth included in the model								
<i>S. mansoni</i> KK (n=2187)			0.34 (-0.84, 1.51)	0.567	2.17 (1.15, 3.18)	<0.001	1.71 (0.59, 2.84)	0.004
<i>S. mansoni</i> PCR (n=2172)			0.38 (-0.72, 1.48)	0.492	2.10 (1.15, 3.05)	<0.001	1.73 (0.65, 2.80)	0.002
<i>S. mansoni</i> intensity KK (n=2187)			0.32 (-0.88, 1.51)	0.596	2.15 (1.11, 3.18)	<0.001	1.67 (0.54, 2.80)	0.005
<i>T. trichiura</i> KK (n=2187)			0.35 (-0.84, 1.54)	0.554	1.97 (0.97, 2.97)	<0.001	1.55 (0.46, 2.63)	0.006
Hookworm PCR (n=2054)			0.51 (-0.66, 1.69)	0.385	2.08 (1.07, 3.09)	<0.001	1.70 (0.59, 2.80)	0.003
<i>S. stercoralis</i> PCR (n=2171)			0.57 (-0.60, 1.74)	0.330	2.08 (1.08, 3.08)	<0.001	1.71 (0.60, 2.82)	0.003
Any worm (n=2122)			0.29 (-0.79, 1.36)	0.592	2.00 (1.06, 2.94)	<0.001	1.62 (0.59, 2.65)	0.003
<b>Body mass index (kg/m<sup>2</sup>)</b>	23.40	23.83	0.43 (-0.12, 0.97)	0.12	0.81 (0.40, 1.23)	<0.001	0.60 (0.10, 1.10)	0.020
With each helminth included in the model								
<i>S. mansoni</i> KK (n=2158)			0.19 (-0.38, 0.76)	0.499	0.88 (0.43, 1.34)	<0.001	0.71 (0.11, 1.31)	0.021
<i>S. mansoni</i> PCR (n=2143)			0.18 (-0.40, 0.76)	0.535	0.80 (0.31, 1.29)	0.002	0.64 (0.01, 1.27)	0.046
<i>S. mansoni</i> intensity KK (n=2158)			0.20 (-0.38, 0.77)	0.496	0.89 (0.43, 1.35)	<0.001	0.72 (0.11, 1.32)	0.022
<i>T. trichiura</i> KK (n=2158)			0.39 (-0.17, 0.95)	0.166	0.81 (0.37, 1.25)	0.001	0.64 (0.06, 1.22)	0.032
Hookworm PCR (n=2027)			0.48 (-0.09, 1.05)	0.094	0.87 (0.41, 1.34)	<0.001	0.73 (0.14, 1.33)	0.017
<i>S. stercoralis</i> PCR (n=2142)			0.43 (-0.14, 1.00)	0.136	0.83 (0.37, 1.29)	0.001	0.67 (0.09, 1.25)	0.024
Any worm (n=2094)			0.23 (-0.35, 0.81)	0.436	0.81 (0.34, 1.28)	0.001	0.67 (0.06, 1.28)	0.033

HOMA-IR, Homeostatic model assessment of insulin resistance; GM, geometric means; P values obtained from survey design-based linear regression; \*Adjusted for age and sex; \*\*Adjusted for age, sex, exercise, alcohol intake and smoking; HOMA-IR, fasting glucose, triglycerides, LDL-cholesterol, HDL-cholesterol, systolic and diastolic BP were additionally adjusted for BMI.

In our relatively young study population, the prevalence of diabetes was low in both settings. It was surprising to find a higher mean fasting glucose and insulin resistance and lower pancreatic beta cell function in the rural setting. Although a higher diabetes prevalence in a rural setting compared to the urban setting has been reported in a study among secondary school students in Cameroon, there was no significant difference in mean fasting glucose in that study<sup>35</sup>. One possible explanation for our finding is occupational. The majority of our rural population is involved in fishing and fishing is mainly conducted at night. Night shift work has been associated with changes in the diurnal pattern of cortisol and consequently predicts increased concentrations of cortisol<sup>36</sup>. Higher cortisol levels have been associated with raised plasma glucose and insulin resistance<sup>37,38</sup>. Shift work has been linked to an increased risk of diabetes<sup>39</sup>, therefore, it is important to study how night time work in these rural fishing communities impacts metabolic health. Also, in view of their occupation, we cannot rule out the possibility that individuals in the rural setting were less adherent to the instructions on overnight fasting before the blood draw.

Another possible explanation is derived from the “thrifty phenotype hypothesis”, which proposes a link between poor fetal and early postnatal nutrition, and the development of T2D in adulthood<sup>40</sup>. This hypothesis proposes that malnutrition in early life impedes development of the pancreas making the pancreas more susceptible to development of diabetes. Therefore, individuals who have spent their early life in rural areas (as most of the rural survey participants had done in this study), where undernutrition is more common, are more prone to glucose dysregulation.

The prevalence of hypertension was low in both settings. The rural environment was protective against hypertension, as suggested by the lower mean blood pressure and lower hypertension prevalence. This is in agreement with previous findings in Uganda and the region<sup>41,42</sup>. Taking into account the higher levels of physical activity and lower BMI among the rural participants in our study did not alter the result, neither did adjusting for smoking and alcohol intake. This implies that other protective factors associated with the rural environment, not measured in our study, such as lower sodium intake<sup>43</sup> and less pollution could be responsible for this. However, modernisation and change in household income may overturn the protective effects of the rural environment. For example, sodium intake in rural and urban Malawi is higher than the recommended amounts<sup>44</sup>. Studies to investigate the trends in cardiometabolic risk factors in rural environments such as the fishing communities we studied are therefore important.

The rural-urban differences we observed in glucose metabolism, blood pressure and BMI could not be explained by the differences in current helminth prevalence. Given the existence of helminth infection in both settings, this is not surprising. The exposure to helminth infection in this particular urban setting (a peninsula, with easy access to the lake) was perhaps not low enough to eliminate helminth effects. Immunological

changes induced by helminths can persist for long periods after clearance of the helminths<sup>45</sup>. Lifestyle factors and other environmental exposures may be having a stronger influence on metabolic outcomes than helminths. However, investigating the role of helminths in the epidemiological transition still remains an important and interesting prospect worth pursuing. Indeed, our previous LaVIISWA trial and observational analyses suggested that schistosomiasis infection was associated with lower serum total cholesterol and LDL-cholesterol levels and that moderate to heavy *S. mansoni* infection was associated with lower triglycerides, LDL-cholesterol and diastolic blood pressure levels. Intensive anthelmintic treatment resulted in higher LDL-cholesterol levels, although helminths were still present in this intensively treated group, albeit with lower intensity than in residents of villages who received standard anthelmintic treatment<sup>22</sup>. Further work in an area with lower helminth prevalence is required to investigate this hypothesis.

The strengths of our project include the large sample size and the uniqueness of the study settings in relation to helminth prevalence. However, we were limited by the cross-sectional nature of the study and therefore cannot make causal inferences from the results, and cannot investigate the longevity, in the context of lifestyle and epidemiological changes, of the observed differences. We performed multiple tests and did not formally correct for this, so cannot rule out chance findings, but all analyses were pre-planned and consistency between glucose and HOMA-IR and between diastolic and systolic blood pressure lend weight to the findings. Differences in socioeconomic status and diet were not assessed and it is possible that these might partially explain differences between rural and urban settings. Fishing communities are rather unique rural communities in relation to housing, lifestyle, diet and exposure to schistosomiasis, and may not be representative of all rural communities.

In conclusion, our findings raise important questions about blood glucose and the rural environment. Is the rural environment potentially detrimental to glucose metabolism? Will the source of the next epidemic of diabetes be the rural areas even when the rural environment still remains associated with a better blood pressure and anthropometric profile?

## Data availability

### Underlying data

LSHTM Data compass: Contrasting impact of rural, versus urban, living on glucose metabolism and blood pressure in Uganda. <https://doi.org/10.17037/DATA.00001528><sup>26</sup>.

This project contains the following underlying data:

- Rural-urban\_survey\_data.csv (individual-level rural-urban survey data).
- Rural-urban\_survey\_data\_codebook.html (codebook for Rural-urban survey data; also lists all questions asked of study participants).

Data are available under the terms of the [Creative Commons Attribution 3.0 International license](https://creativecommons.org/licenses/by/3.0/) (CC-BY 3.0).

## Acknowledgements

We thank the community members of Koome sub-county and Entebbe Municipality, their local council leaders and village health team members for participating in these studies. We thank the leadership of Mukono and Wakiso Districts and particularly the district health officer – Mukono (Elly Tumushabe) and the

councillor for Koome sub-county (Asuman Muwumuza), who are members of the LaVIISWA Trial Steering Committee (TSC), for their support. We also thank also the other members of the TSC: Heiner Grosskurth (chair), Edridah Tukahebwa, Narcis Kabatereine, Neil Pearce, Anatoli Kamali and Monica Kuteesa. We are grateful to Moffat Nyirenda, who is a member of Richard Sanya's doctoral committee, for his guidance and support.

## References

- GBD 2016 Causes of Death Collaborators: **Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016.** *Lancet.* 2017; **390**(10100): 1151–210.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- GBD 2016 DALYs and HALE Collaborators: **Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016.** *Lancet.* 2017; **390**(10100): 1260–344.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Noncommunicable diseases country profiles 2018.** Geneva: World Health Organisation; 2018.  
[Reference Source](#)
- Patel RB, Burke TF: **Urbanization--an emerging humanitarian disaster.** *N Engl J Med.* 2009; **361**(8): 741–3.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- International Diabetes Federation: **IDF Diabetes Atlas.** 8th ed. 2017.  
[Reference Source](#)
- Angkurawaranon C, Wisetborisut A, Rerkasem K, et al.: **Early life urban exposure as a risk factor for developing obesity and impaired fasting glucose in later adulthood: results from two cohorts in Thailand.** *BMC Public Health.* 2015; **15**: 902.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Yusuf S, Rangarajan S, Teo K, et al.: **Cardiovascular risk and events in 17 low-, middle-, and high-income countries.** *N Engl J Med.* 2014; **371**(9): 818–27.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Kavishe B, Biraro S, Baisley K, et al.: **High prevalence of hypertension and of risk factors for non-communicable diseases (NCDs): a population based cross-sectional survey of NCDs and HIV infection in Northwestern Tanzania and Southern Uganda.** *BMC Med.* 2015; **13**: 126.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Chiwanga FS, Njelekela MA, Diamond MB, et al.: **Urban and rural prevalence of diabetes and pre-diabetes and risk factors associated with diabetes in Tanzania and Uganda.** *Glob Health Action.* 2016; **9**(1): 31440.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Fezeu L, Kengne AP, Balkau B, et al.: **Ten-year change in blood pressure levels and prevalence of hypertension in urban and rural Cameroon.** *J Epidemiol Community Health.* 2010; **64**(4): 360–5.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Guwatudde D, Mutungi G, Wesonga R, et al.: **The Epidemiology of Hypertension in Uganda: Findings from the National Non-Communicable Diseases Risk Factor Survey.** *PLoS One.* 2015; **10**(9): e0138991.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- NCD Risk Factor Collaboration (NCD-RisC). **Rising rural body-mass index is the main driver of the global obesity epidemic in adults.** *Nature.* 2019; **569**(7755): 260–4.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Rook GAW: **99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: darwinian medicine and the 'hygiene' or 'old friends' hypothesis.** *Clin Exp Immunol.* 2010; **160**(1): 70–9.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Donath MY, Shoelson SE: **Type 2 diabetes as an inflammatory disease.** *Nat Rev Immunol.* 2011; **11**(2): 98–107.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Gisterå A, Hansson GK: **The immunology of atherosclerosis.** *Nat Rev Nephrol.* 2017; **13**(6): 368–80.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Solak Y, Afsar B, Vaziri ND, et al.: **Hypertension as an autoimmune and inflammatory disease.** *Hypertens Res.* 2016; **39**(8): 567–73.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Tracey EF, McDermott RA, McDonald MI: **Do worms protect against the metabolic syndrome? A systematic review and meta-analysis.** *Diabetes Res Clin Pract.* 2016; **120**: 209–20.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Gurven MD, Trumble BC, Stieglitz J, et al.: **Cardiovascular disease and type 2 diabetes in evolutionary perspective: a critical role for helminths?** *Evol Med Public Health.* 2016; **2016**(1): 338–57.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Berbudi A, Ajendra J, Wardani AP, et al.: **Parasitic helminths and their beneficial impact on type 1 and type 2 diabetes.** *Diabetes Metab Res Rev.* 2016; **32**(3): 238–50.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Nampijja M, Webb EL, Kaweesa J, et al.: **The Lake Victoria Island Intervention Study on Worms and Allergy-related diseases (LaVIISWA): study protocol for a randomised controlled trial.** *Trials.* 2015; **16**: 187.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Uganda Bureau of Statistics: **The National Population and Housing Census 2014 – Sub-County Report.** Kampala, Uganda. 2016.  
[Reference Source](#)
- Sanya RE, Webb EL, Zziwa C, et al.: **The effect of helminth infections and their treatment on metabolic outcomes: results of a cluster-randomised trial.** *Clin Infect Dis.* 2019; pii: ciz859.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Nkurunungi G, Lubyayi L, Versteeg SA, et al.: **Do helminth infections underpin urban-rural differences in risk factors for allergy-related outcomes?** *Clin Exp Allergy.* 2019; **49**(5): 663–76.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Nkurunungi G, van Diepen A, Nassuuna J, et al.: **Microarray assessment of N-glycan-specific IgE and IgG profiles associated with *Schistosoma mansoni* infection in rural and urban Uganda.** *Sci Reps.* 2019; **9**(1): 3522.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Uganda Bureau of Statistics: **The National Population and Housing Census 2014 – Main Report.** Kampala, Uganda: Uganda Bureau of Statistics. 2016.  
[Reference Source](#)
- Sanya R, Webb E: **Contrasting impact of rural, versus urban, living on glucose metabolism and blood pressure in Uganda.** [Data Collection]. London School of Hygiene & Tropical Medicine, London, United Kingdom, 2019. <http://www.doi.org/10.17037/DATA.00001528>
- Melrose WD, Turner PF, Pisters P, et al.: **An improved Knott's concentration test for the detection of microfilariae.** *Trans R Soc Trop Med Hyg.* 2000; **94**(2): 176.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Katz N, Chaves A, Pellegrino J: **A simple device for quantitative stool thick-smear technique in *Schistosomiasis mansoni*.** *Rev Inst Med Trop Sao Paulo.* 1972; **14**(6): 397–400.  
[PubMed Abstract](#)
- Verweij JJ, Brienen EA, Ziem J, et al.: **Simultaneous detection and quantification of *Ancylostoma duodenale*, *Necator americanus*, and *Oesophagostomum bifurcum* in fecal samples using multiplex real-time PCR.** *Am J Trop Med Hyg.* 2007; **77**(4): 685–90.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Verweij JJ, Canales M, Polman K, et al.: **Molecular diagnosis of *Strongyloides stercoralis* in faecal samples using real-time PCR.** *Trans R Soc Trop Med Hyg.* 2009; **103**(4): 342–6.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- World Health Organisation: **Global Report on Diabetes.** Geneva, Switzerland. 2016.  
[Reference Source](#)
- World Health Organisation / International Diabetes Federation: **Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia.** Geneva, Switzerland. 2006.  
[Reference Source](#)

33. Whelton PK, Carey RM, Aronow WS, *et al.*: **2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.** *J Am Coll Cardiol.* 2018; **71**(19): e127–e248.  
[PubMed Abstract](#) | [Publisher Full Text](#)
34. Falkner B, Daniels SR: **Summary of the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.** *Hypertension.* 2004; **44**(4): 387–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
35. Kamdem F, Lemogoum D, Jingi AM, *et al.*: **Prevalence and determinants of abnormal glucose metabolism in urban and rural secondary schools in Cameroon: A cross-sectional study in a sub-Saharan Africa setting.** *Prim Care Diabetes.* 2019; **13**(4): 370–375.  
[PubMed Abstract](#) | [Publisher Full Text](#)
36. Li J, Bidlingmaier M, Petru R, *et al.*: **Impact of shift work on the diurnal cortisol rhythm: a one-year longitudinal study in junior physicians.** *J Occup Med Toxicol.* 2018; **13**: 23.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
37. Phillips DI, Barker DJ, Fall CH, *et al.*: **Elevated plasma cortisol concentrations: a link between low birth weight and the insulin resistance syndrome?** *J Clin Endocrinol Metab.* 1998; **83**(3): 757–60.  
[PubMed Abstract](#) | [Publisher Full Text](#)
38. Misra M, Bredella MA, Tsai P, *et al.*: **Lower growth hormone and higher cortisol are associated with greater visceral adiposity, intramyocellular lipids, and insulin resistance in overweight girls.** *Am J Physiol Endocrinol Metab.* 2008; **295**(2): E385–92.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
39. Gan Y, Yang C, Tong X, *et al.*: **Shift work and diabetes mellitus: a meta-analysis of observational studies.** *Occup Environ Med.* 2015; **72**(1): 72–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
40. Hales CN, Barker DJ: **Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis.** *Diabetologia.* 1992; **35**(7): 595–601.  
[PubMed Abstract](#) | [Publisher Full Text](#)
41. Price AJ, Crampin AC, Amberbir A, *et al.*: **Prevalence of obesity, hypertension, and diabetes, and cascade of care in sub-Saharan Africa: a cross-sectional, population-based study in rural and urban Malawi.** *Lancet Diabetes Endocrinol.* 2018; **6**(3): 208–22.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
42. Guwatudde D, Nankya-Mutyoba J, Kalyesubula R, *et al.*: **The burden of hypertension in sub-Saharan Africa: a four-country cross sectional study.** *BMC Public Health.* 2015; **15**: 1211.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
43. Mizehoun-Adissoda C, Houinato D, Houehanou C, *et al.*: **Dietary sodium and potassium intakes: Data from urban and rural areas.** *Nutrition.* 2017; **33**: 35–41.  
[PubMed Abstract](#) | [Publisher Full Text](#)
44. Prynne JE, Banda L, Amberbir A, *et al.*: **Dietary sodium intake in urban and rural Malawi, and directions for future interventions.** *Am J Clin Nutr.* 2018; **108**(3): 587–93.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
45. Soonawala D, Geerts JW, de Mos M, *et al.*: **The immune response to schistosome antigens in formerly infected travelers.** *Am J Trop Med Hyg.* 2011; **84**(1): 43–7.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

# Open Peer Review

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## Version 2

Reviewer Report 25 August 2020

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**Michael D. Gurven** 

Department of Anthropology, University of California, Santa Barbara, Santa Barbara, CA, USA

The authors did a good job addressing my comments.

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Evolutionary anthropology, indigenous health.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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## Version 1

Reviewer Report 06 April 2020

<https://doi.org/10.21956/wellcomeopenres.17107.r38188>

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**Bruno Guigas** 

Department of Parasitology, Leiden University Medical Center, Leiden, The Netherlands

In the present manuscript, Sanya *et al.* have conducted a cross-sectional study comparing various metabolic parameters in both rural and urban communities in Uganda for investigating the potential impact of helminth infection and living environment on cardiometabolic diseases. Altogether, after multiple adjustments, they found that individuals living in rural environment

have a lower blood pressure than urban ones, as previously reported in other studies conducted in different countries, but a surprisingly higher fasting glucose levels and HOMA-IR despite lower incidence of type 2 diabetes. Helminth infection seems not to have any significant impact on all these parameters but, as acknowledged by the authors, individuals living in urban environment have a rather high rates of infection/treatment with anthelmintic drugs, suggesting that previous exposure might have already triggered/imprinted some immune response potentially beneficial for metabolic homeostasis.

The design of the study is solid and the large sample size available, together with subtle diagnosis of helminths infection, is clearly one of the strength of such approach. The main weakness relies on the significant differences in gender and age distribution between rural and urban communities, especially for young participants (<19 year-old; 11.8% versus 28%, respectively;  $p < 0.001$ ). I'd have been curious to see whether the main outcomes were still present if the analyses have been systematically done only in adults.

I have some minor comments/questions:

- I'd suggest reporting the raw data for BMI and fasting insulin levels (used to calculate HOMA-IR) in Table 1 and 2, respectively.
- To try explaining the counterintuitive higher fasting glucose levels in individuals living in rural environment, the authors suggested that early life malnutrition in such population might affect pancreas development and predispose to metabolic dysfunctions. As such, it would have been interesting to calculate HOMA-B ( $20 \times \text{fasting insulin } (\mu\text{IU/ml}) / \text{fasting glucose (mmol/ml)} - 3.5$ ), which is a widely used index for assessing pancreatic beta cell function in humans.
- The discussion around the impact of disturbances in circadian rhythms, notably of cortisol levels, on glucose homeostasis due to nocturnal fishing activities in rural communities is definitely relevant. But it also raises a question about the eventual compliance to fasting for blood collection in such conditions. Could the authors provide a bit more information about the nutritional guidelines provided to the subjects prior to blood collection (last meal, sugar beverages...)? Same thing concerning the moment of the day where the blood pressure was measured.
- I'm not sure the term "impair glucose metabolism" used in the conclusion of the abstract is the most appropriate since both fasting plasma glucose levels and HOMA-IR, although higher in individuals living in rural than urban areas, are still far from the pathological ranges.

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

I cannot comment. A qualified statistician is required.

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Molecular pathophysiology of metabolic diseases; Immunometabolism.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Author Response 18 Aug 2020

**Richard Sanya**, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda

The authors thank the reviewer for the comments on the manuscript and respond as follows.

**Comment:** In the present manuscript, Sanya *et al.* have conducted a cross-sectional study comparing various metabolic parameters in both rural and urban communities in Uganda for investigating the potential impact of helminth infection and living environment on cardiometabolic diseases. Altogether, after multiple adjustments, they found that individuals living in rural environment have a lower blood pressure than urban ones, as previously reported in other studies conducted in different countries, but a surprisingly higher fasting glucose levels and HOMA-IR despite lower incidence of type 2 diabetes. Helminth infection seems not to have any significant impact on all these parameters but, as acknowledged by the authors, individuals living in urban environment have a rather high rates of infection/treatment with anthelmintic drugs, suggesting that previous exposure might have already triggered/imprinted some immune response potentially beneficial for metabolic homeostasis.

The design of the study is solid and the large sample size available, together with subtle diagnosis of helminths infection, is clearly one of the strength of such approach. The main weakness relies on the significant differences in gender and age distribution between rural and urban communities, especially for young participants (<19 year-old; 11.8% versus 28%, respectively;  $p < 0.001$ ). I'd have been curious to see whether the main outcomes were still present if the analyses have been systematically done only in adults.

**Response:** Following the reviewer's suggestion, we did the analysis only in adults ([table 3](#)) and still found the differences in blood pressure and BMI. However, the differences in fasting glucose and HOMA-IR were less apparent, albeit with wider confidence intervals due

to the reduction in sample size.

**Comment:** I have some minor comments/questions:

**Comment:** I'd suggest reporting the raw data for BMI and fasting insulin levels (used to calculate HOMA-IR) in Table 1 and 2, respectively.

**Response:** Data on the mean BMI in both populations are reported in table 2 and on the weight categories classified according to BMI in table 4. In the revised version of the manuscript, we have included the mean insulin levels in table 2.

**Comment:** To try explaining the counterintuitive higher fasting glucose levels in individuals living in rural environment, the authors suggested that early life malnutrition in such population might affect pancreas development and predispose to metabolic dysfunctions. As such, it would have been interesting to calculate HOMA-B ( $20 \times \text{fasting insulin } (\mu\text{IU/ml}) / \text{fasting glucose (mmol/ml)} - 3.5$ ), which is a widely used index for assessing pancreatic beta cell function in humans.

**Response:** We calculated the mean pancreatic beta cell function in the two populations using the formula above. We found that individuals in the urban setting had higher (better) pancreatic beta cell function (HOMA-B) than individuals in the rural setting even after adjusting for age, sex, exercise, alcohol intake, smoking and BMI (141.34 vs 201.72; adjusted mean difference 40.36 [95% confidence interval 8.00, 72.72]  $p=0.02$ ). This has been included in the revised manuscript.

**Comment:** The discussion around the impact of disturbances in circadian rhythms, notably of cortisol levels, on glucose homeostasis due to nocturnal fishing activities in rural communities is definitely relevant. But it also raises a question about the eventual compliance to fasting for blood collection in such conditions. Could the authors provide a bit more information about the nutritional guidelines provided to the subjects prior to blood collection (last meal, sugar beverages...)? Same thing concerning the moment of the day where the blood pressure was measured.

**Response:** The discussion has been revised to include the possibility of non-compliance to overnight fasting. However, all participants were told to fast from food and drink overnight for at least 8 hours and not to exercise or smoke before sample collection in the morning. Plain water could be consumed as much and as often as desired.

**Comment:** I'm not sure the term "impair glucose metabolism" used in the conclusion of the abstract is the most appropriate since both fasting plasma glucose levels and HOMA-IR, although higher in individuals living in rural than urban areas, are still far from the pathological ranges.

**Response:** We have revised the conclusion to reflect this.

**Competing Interests:** No competing interests were disclosed.

Reviewer Report 06 April 2020

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**Michael D. Gurven** 

Department of Anthropology, University of California, Santa Barbara, Santa Barbara, CA, USA

This large-scale cross-sectional study compares urban and rural Ugandans in several measures of cardiometabolic health risk. It highlights one salient aspect of many rural environments - intestinal helminthic infections - to test whether having helminths is associated with better cardiometabolic health. This follows from a small but growing literature that has proposed the intriguing hypothesis that helminths might offer protection against insulin resistance, hypercholesterolemia, hypertension and other factors underlying diabetes and atherosclerosis risk. While the authors find urban-rural differences in the majority of health outcomes, they do not find any evidence that helminths mediate these differences.

As the authors indicate, helminth infection is highly prevalent in both rural and urban settings, and so there is no helminth-free control comparison. While helminths do not explain any urban-rural differences in cardiometabolic health, it is possible that helminth infection is still associated with lower blood glucose, lower blood pressure and other health variables – just that these effects are similar across the urban-rural divide. Those analyses are not reported here. But a prior paper by this same research team working in Uganda (Sanya *et al.* 2019<sup>1</sup>) does a better job of directly testing the helminth hypothesis by comparing those who received a standard antihelminth treatment with those receiving a more intensive pharmacological treatment regime. While that paper also did not have a helminth-free control, it did show that more frequent antihelminth treatment resulted in lower LDL and total cholesterol. Having a heavier *Schistosoma mansoni* infectious burden was also associated with lower blood triglyceride levels and lower diastolic blood pressure. It is curious that these rich findings by the same team are not highlighted or contextualized in the current study.

I wonder if the Kato Katz analysis of infection intensity gives any more traction than the binary presence/absence used in the paper. Given most people have low-level burden, is it the case that protective effects are more evident among those with heavier burden? Given the cross-sectional nature of the database, however, those with heavier worm burden may have other health deficits or be living under more resource-poor and compromised setting. Additional controls for socioeconomic status may help adjust for potential confounding.

As for the urban-rural health differences, the authors show that urban areas have higher diabetes risk (but lower fasting blood glucose), and higher prevalence of hypertension and obesity – though it is worth noting that overall prevalence of these conditions is low in both settings, and that ~77% of their sample consists of people under age 40. Perhaps due to the small absolute differences between setting, they find no urban-rural differences in metabolic syndrome—itsself just a combination of the other cardiometabolic biomarkers.

The emphasis on urban-rural health differences is a useful starting point, but itself does not explain much, and may not generalize to other regions or countries. The authors conclude in the Abstract: "In low-income countries, rural living may protect against hypertension but impair glucose metabolism". What is the basis for making such a broad generalization? "Urban" or "rural" are proxies for a cluster of traits that directly impact health, including diet, lifestyle differences (e.g. alcohol, smoking), physical activity, infection, social cohesion, pollution exposure, and the like. In the Ugandan context here, there are some patterns that do not generalize to many other urban-rural comparisons. For example, smoking and alcohol consumption appear to be more common in the rural than the urban context. Underweight is more prevalent in the urban setting, and this urban setting has lower but non-trivial prevalence of infection by several helminth species. These characteristics will vary widely across regions and countries. In order to generalize you would expect to find consistent differences across the key domains relevant to cardiometabolic disease: diet, physical activity, lifestyle, infection, etc.

Given that urban-rural health differences still exist in their fully adjusted models, what can one conclude as to why? The first possibility is what might be missing from the adjusted models. The most obvious missing variable(s) reflect diet. It was a shame that diet was not assessed (or even described in a general way), including additives like sugar, salt and oil, and consumption of processed foods and beverages. Physical activity was also not measured directly, though participants were asked about "exercise and vigorous activity". Exercise may be construed as a bit of a luxury, and vigorous activity is indicative but may not be the most relevant for comparison. What is more telling is how much moderate activity vs. sedentary activity people engage in through their daily activities – not restricted to leisure or exercise. Even without activity directly measured (e.g. with accelerometry), it's possible that occupation might give a better indication of habitual activity than the interview question on exercise/vigorous activity. Perhaps adjustment for livelihood would contribute towards explaining (at least statistically) the urban-rural health differences.

Another question is how long the current differences between urban and rural contexts have existed? If some lifestyle changes are recent, there might be greater health differences across urban-rural contexts among the younger cohorts. In this case, there would be an interaction between age cohort and urban-rural difference. Similarly, is there a sex difference in exposures due to how modernization manifests? I noticed that the urban sample was much more female-biased, suggesting male out-migration or wage labor leading to greater male absenteeism.

The authors mention the thrifty phenotype as a possible explanation for why people in the rural areas might be prone to glucose dysregulation. Thrifty phenotype and developmental origins of health and disease (DOHaD) paradigms emphasize the effects of early life exposures on later life chronic disease risk, especially when conditions shift over the life course (e.g. from harsh to abundant). That one-third of those living in the urban context were born and spent their first five years of life in a rural area permits one to explore the potential effects of developmental plasticity. A "purer" urban-rural contrast would be limited to those who spent their entire lives in the same environmental context. An additional exploration could test whether those who spent their early life in a rural context but now live in an urban context show worse cardiometabolic health than those who have spent their entire lives in a rural context. The authors have the data to make these comparisons, but do not include these early life variables in any analyses other than sample description (Table 1).

Lastly, while the authors speculate that sleep disruption and altered circadian rhythms might explain the surprising finding that fasting glucose is higher in the rural context, a simpler (but less interesting) possibility is that people in a rural context may be less likely to adhere to the requirement of an overnight fast prior to blood draw (especially if as noted, night fishing is a common activity in the rural setting). In the future, glycosylated hemoglobin (HbA1c) could be measured to provide a more reliable, long-term indicator of glucose levels.

Also, although maybe less relevant, it was unclear whether there are ethnic differences within or between sampling areas that might reflect genetic differences underlying health risk.

Overall, this is a nice epidemiological study highlighting imminent chronic disease risks in Uganda, showcasing that such risks are not restricted to urban areas. Prevalence rates of hypertension and central obesity are noteworthy in both urban and rural contexts.

Minor:

Given lower response rate due to absenteeism in the urban sample, are absent individuals more or less likely to show any health differences than those at home (e.g. more involved in wage labor, and perhaps more integrated into market economy)? If data exist for only one round of data collection then maybe this potential for bias cannot be checked.

Any current use of medications, e.g. for hypertension? If so, are those individuals excluded from analyses of biomarkers?

### References

1. Sanya RE, Webb EL, Zziwa C, Kizindo R, et al.: The effect of helminth infections and their treatment on metabolic outcomes: results of a cluster-randomised trial. *Clin Infect Dis*. 2019. [PubMed Abstract](#) | [Publisher Full Text](#)

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Yes

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Evolutionary anthropology, indigenous health.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 18 Aug 2020

**Richard Sanya**, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda

The authors thank the reviewer for the comments on the manuscript and respond as follows.

**Comment:** This large-scale cross-sectional study compares urban and rural Ugandans in several measures of cardiometabolic health risk. It highlights one salient aspect of many rural environments - intestinal helminthic infections - to test whether having helminths is associated with better cardiometabolic health. This follows from a small but growing literature that has proposed the intriguing hypothesis that helminths might offer protection against insulin resistance, hypercholesterolemia, hypertension and other factors underlying diabetes and atherosclerosis risk. While the authors find urban-rural differences in the majority of health outcomes, they do not find any evidence that helminths mediate these differences.

As the authors indicate, helminth infection is highly prevalent in both rural and urban settings, and so there is no helminth-free control comparison. While helminths do not explain any urban-rural differences in cardiometabolic health, it is possible that helminth infection is still associated with lower blood glucose, lower blood pressure and other health variables - just that these effects are similar across the urban-rural divide. Those analyses are not reported here. But a prior paper by this same research team working in Uganda (Sanya *et al.* 2019<sup>1</sup>) does a better job of directly testing the helminth hypothesis by comparing those who received a standard antihelminth treatment with those receiving a more intensive pharmacological treatment regime. While that paper also did not have a helminth-free control, it did show that more frequent antihelminth treatment resulted in lower LDL and total cholesterol. Having a heavier *Schistosoma mansoni* infectious burden was also associated with lower blood triglyceride levels and lower diastolic blood pressure. It is curious that these rich findings by the same team are not highlighted or contextualized in the current study.

**Response:** Thank you for this suggestion. We agree that helminth infection may still be associated with lower blood glucose and other health variables. Following the reviewer's suggestion, in the new version of the manuscript, we have incorporated our previous findings into the fifth paragraph of the discussion, and highlight that the potential role of helminths in the epidemiological transition merits further investigation.

**Comment:** I wonder if the Kato Katz analysis of infection intensity gives any more traction than the binary presence/absence used in the paper. Given most people have low-level burden, is it the case that protective effects are more evident among those with heavier burden? Given the cross-sectional nature of the database, however, those with heavier worm burden may have other health deficits or be living under more resource-poor and compromised setting. Additional controls for socioeconomic status may help adjust for potential confounding.

**Response:** Thank you for this suggestion. We have redone the analysis and included *S. mansoni* infection intensity in the revised manuscript (Table 5). *S. mansoni* infection intensity did not explain the rural-urban differences, and we have expanded the text in the last paragraph of the results section to include this finding. Unfortunately, we did not collect data on socio-economic status in the metabolic survey conducted in the rural setting and were therefore unable to adjust for it in this analysis. We now state this in the discussion (paragraph 6) as a limitation of the study.

**Comment:** As for the urban-rural health differences, the authors show that urban areas have higher diabetes risk (but lower fasting blood glucose), and higher prevalence of hypertension and obesity – though it is worth noting that overall prevalence of these conditions is low in both settings, and that ~77% of their sample consists of people under age 40. Perhaps due to the small absolute differences between setting, they find no urban-rural differences in metabolic syndrome—itsself just a combination of the other cardiometabolic biomarkers.

**Response:** Thank you for pointing this out. The overall prevalence of diabetes and hypertension was low in both settings and the majority of the population was young. We have now highlighted the relatively young study population (representative of the country as a whole) in the discussion. We had previously stated in the discussion that the prevalence of diabetes was low in both settings, but have now included a similar statement about hypertension in the revised manuscript.

**Comment:** The emphasis on urban-rural health differences is a useful starting point, but itself does not explain much, and may not generalize to other regions or countries. The authors conclude in the Abstract: “In low-income countries, rural living may protect against hypertension but impair glucose metabolism”. What is the basis for making such a broad generalization? “Urban” or “rural” are proxies for a cluster of traits that directly impact health, including diet, lifestyle differences (e.g. alcohol, smoking), physical activity, infection, social cohesion, pollution exposure, and the like. In the Ugandan context here, there are some patterns that do not generalize to many other urban-rural comparisons. For example, smoking and alcohol consumption appear to be more common in the rural than the urban context. Underweight is more prevalent in the urban setting, and this urban setting has lower but non-trivial prevalence of infection by several helminth species. These characteristics will vary widely across regions and countries. In order to generalize you would expect to find consistent differences across the key domains relevant to cardiometabolic disease: diet, physical activity, lifestyle, infection, etc.

**Response:** We appreciate the reviewer’s point and have refined the conclusion to make it

more specific. It now reads “In the Ugandan context, living in rural fishing communities may protect against hypertension but worsen glucose metabolism”.

**Comment:** Given that urban-rural health differences still exist in their fully adjusted models, what can one conclude as to why? The first possibility is what might be missing from the adjusted models. The most obvious missing variable(s) reflect diet. It was a shame that diet was not assessed (or even described in a general way), including additives like sugar, salt and oil, and consumption of processed foods and beverages. Physical activity was also not measured directly, though participants were asked about “exercise and vigorous activity”. Exercise may be construed as a bit of a luxury, and vigorous activity is indicative but may not be the most relevant for comparison. What is more telling is how much moderate activity vs. sedentary activity people engage in through their daily activities – not restricted to leisure or exercise. Even without activity directly measured (e.g. with accelerometry), it’s possible that occupation might give a better indication of habitual activity than the interview question on exercise/vigorous activity. Perhaps adjustment for livelihood would contribute towards explaining (at least statistically) the urban-rural health differences.

**Response:** In the second last paragraph of the discussion, we acknowledged the absence of data on diet as a limitation and have stated, in the revised manuscript, that the differences in the rural and urban settings may be partially explained by diet and socio-economic status, and that not being able to adjust for these factors is a limitation of the study. Following the reviewer’s suggestion, we have redone the analysis and added occupation as a possible proxy for activity levels to the adjusted models. No major differences were observed between the findings from the adjusted model and those in the previous model without the occupation variable. The results of the adjusted model are presented in the new version of the manuscript.

**Comment:** Another question is how long the current differences between urban and rural contexts have existed? If some lifestyle changes are recent, there might be greater health differences across urban-rural contexts among the younger cohorts. In this case, there would be an interaction between age cohort and urban-rural difference. Similarly, is there a sex difference in exposures due to how modernization manifests? I noticed that the urban sample was much more female-biased, suggesting male out-migration or wage labor leading to greater male absenteeism.

**Response:** Thank you for this. In view of the cross-sectional nature of the study design, we were unable to determine how long the current differences in metabolic parameters between the rural and urban contexts have existed and to our knowledge, no study has previously assessed the urban-rural differences in metabolic outcomes in these populations. The rural population in particular is highly mobile, with only 9% having lived there all their lives (Table 1), therefore examining for an interaction between age cohort and urban-rural differences may not be informative. We have expanded our discussion to highlight these consequences of the cross-sectional study design.

**Comment:** The authors mention the thrifty phenotype as a possible explanation for why people in the rural areas might be prone to glucose dysregulation. Thrifty phenotype and

developmental origins of health and disease (DOHaD) paradigms emphasize the effects of early life exposures on later life chronic disease risk, especially when conditions shift over the life course (e.g. from harsh to abundant). That one-third of those living in the urban context were born and spent their first five years of life in a rural area permits one to explore the potential effects of developmental plasticity. A “purer” urban-rural contrast would be limited to those who spent their entire lives in the same environmental context. An additional exploration could test whether those who spent their early life in a rural context but now live in an urban context show worse cardiometabolic health than those who have spent their entire lives in a rural context. The authors have the data to make these comparisons, but do not include these early life variables in any analyses other than sample description (Table 1).

**Response:** Exploring the potential effects of plasticity on the metabolic outcomes and the “purer” rural-urban contrast limited to those who spent their entire lives in the same environmental context are excellent suggestions. However, these analyses were not preplanned and the surveys were not powered to measure them. With that in mind, we have performed this posthoc analysis and the results are shown in tables 1 and 2. We did not find differences in HOMA-IR and fasting glucose between individuals in the urban environment who spent their entire lives in the urban environment and those who were born and lived in the rural environment for the first five years and later moved to the urban environment (table 1).

For the “purer” rural-urban analysis limited to individuals who spent their entire lives in the same environment (table 2), we still found differences in fasting glucose and blood pressure, as in the main analysis. However, the difference in HOMA-IR, observed in the main analysis was lost here.

The number of individuals analysed was far smaller than in the main analysis, and this cannot be ruled out as a reason for the discrepancy in the two findings. However, we do appreciate the input and will factor this in when designing rural-urban comparison studies in the future.

**Comment:** Lastly, while the authors speculate that sleep disruption and altered circadian rhythms might explain the surprising finding that fasting glucose is higher in the rural context, a simpler (but less interesting) possibility is that people in a rural context may be less likely to adhere to the requirement of an overnight fast prior to blood draw (especially if as noted, night fishing is a common activity in the rural setting). In the future, glycosylated hemoglobin (HbA1c) could be measured to provide a more reliable, long-term indicator of glucose levels.

**Response:** Thank you for this suggestion - we have revised the manuscript to include this possibility.

**Comment:** Also, although maybe less relevant, it was unclear whether there are ethnic differences within or between sampling areas that might reflect genetic differences underlying health risk.

**Response:** There were no ethnic differences between the sampling areas. This is shown in table 1 where reference is made to parental tribe.

**Comment:** Overall, this is a nice epidemiological study highlighting imminent chronic disease risks in Uganda, showcasing that such risks are not restricted to urban areas. Prevalence rates of hypertension and central obesity are noteworthy in both urban and rural contexts.

Minor:

**Comment:** Given lower response rate due to absenteeism in the urban sample, are absent individuals more or less likely to show any health differences than those at home (e.g. more involved in wage labor, and perhaps more integrated into market economy)? If data exist for only one round of data collection then maybe this potential for bias cannot be checked.

**Response:** Unfortunately, there was only one urban survey. We did not explore the health differences between individuals who were present at home and those absent because the individual questionnaires used to capture these data were only administered to participants who were present.

**Comment:** Any current use of medications, e.g. for hypertension? If so, are those individuals excluded from analyses of biomarkers?

**Response:** Current use of medications especially for hypertension, was uncommon and therefore these individuals were not excluded from the analysis.

**Competing Interests:** No competing interests were disclosed.